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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,278	11/13/2000	Michael Reggelin	147/49227	2959

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1200 G Street NW Suite 700  
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EXAMINER

HUANG, EVELYN MEI

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 01/14/2002

6

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/700,278

Applicant(s)

REGGELIN ET AL.

Examiner

Evelyn Huang

Art Unit

1625

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 17-33 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17-33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                             | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____.  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                    | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____. | 6) <input type="checkbox"/> Other: _____                                    |

Art Unit: 1625

1. Claims 17-33 are pending. Claims 1-16 have been canceled according to the preliminary amendment filed on 11-13-2000.

***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-27, 28, 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- a. Claim 17,

- a) (i), and b), the term 'suitable' is vague; what are the criteria for its suitability? Its deletion is recommended.
- 'if desired' is unclear, replacement with 'optionally' is recommended.

- b. Since dependent Claim 28 recites 'cyclic structure of formula Xa contains a secondary nitrogen atom protected by t-butylcarbonyl protecting group', should the definition of R<sup>901</sup> of the base claim 27 also include a protecting group for the amino? If the answer is negative, then claim 28 would have no antecedent basis of the base claim 27.

- c. Does applicant intend the protected compound of claim 29 wherein R<sup>801</sup> and R<sup>901</sup> together form an alkylene chain to have a quaternary nitrogen?

The rejection is applicable to claims dependent on the above claims.

***Claim Rejections - 35 USC § 102***

3. Assuming that R<sup>901</sup> may also be a protecting group, the following rejection is made.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Art Unit: 1625

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 27 is rejected under 35 U.S.C. 102(a) as being anticipated by Bolte (PTO-1449).  
The compound of Bolte is encompassed by the instant claim.

*Claim Rejections - 35 USC § 103*

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bolte (PTO-1449) in view of Greene.

Bolte discloses the instant compound with a toluenesulfonyl protecting group at the pyrrolinyl nitrogen, whereas the compound of instant claim 28 has a t-butoxycarbonyl protecting group. Toluensulfonyl and t-butoxycarbonyl are art-recognized protecting groups for the amino group (Greene, page 309, 18.; page 327 ; page 313, 49.; page 379).

One of ordinary skill in the art would be motivated to replace the toluenesulfonyl with the alternative t-butoxycarbonyl to arrive at the instant invention since Greene had expressly taught that both of them are optional groups effective for the protection of the amino group.

6. Claims 17-25, 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lash (J. Het. Chem. 1991, PTO-1449) and Reggelin I (Liebigs Ann/Recueil, 1997, PTO-1449) and Reggelin II (J. Am. Chem. Soc. 1996) and Bolte (PTO-1449) in view of Greene.

Lash describes a species of instant formula Ia' (page 1671, scheme 1, compounds 3f, 3h).

While Lash does not teach the instant process, Reggelin I teaches the instant stereoselective synthesis with a metallated 2-alkenyl sulfoximines intermediate (page 1883, Table 1),

Art Unit: 1625

followed by reductive elimination of the sulfur moiety from the S-aminooxosulfonium intermediate for the preparation of a tetrahydrofuranyl compound (Reggeline II, column 1, scheme 17 ; Removal of the Auxillary), which is structurally analogous to the instant pyrrolidinyl compound. The instant pyrrolidinyl intermediate compound is described by Bolte (see paragraphs above).

At the time of the invention, guided by the combined teachings of the prior art, one of ordinary skill in the art would be motivated to prepare Lash's compound by the alternative process of Reggeline I and II using the corresponding intermediate compound as described by Bolte to arrive at the instant invention with the reasonable expectation of obtaining a more efficient process for the stereochemically controlled preparation of an isomerically pure substituted azacyclic compound. To one of ordinary skill in the art, the preparation of a known compound employing known or obvious starting materials via a known or obvious process is *prima facie* obvious in the absence of unexpected results.

While the above references do not specifically disclose the amino-protecting fluoren-9-yl-methoxy-carbonyl as in the instant claim 20, or the hydroxy-protecting trimethylsilyl of the instant claim 25, Greene expressly teaches these protecting groups (page 309, 2.; page 318; page 12, 72.; page 68 ).

At the time of the invention, one of ordinary skill in the art would be motivated to temporarily block the other reactive sites employing the art-known protecting group as taught by Greene to ensure the selective reaction at the desired reactive site.

### ***Claim Rejections - 35 USC § 112***

7. Claims 17-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is being enabling only for the synthesis of compounds wherein  $R^1$ ,  $R^2$ ,  $R^{5-7}$ ,  $R^3$  and  $R^4$  are individual substituents or  $R^3$  and  $R^4$  together form a  $C_{3-4}$  alkylene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. *Nature of the invention.*

Art Unit: 1625

The instant invention is drawn to a stereochemically controlled preparation of an isomerically pure substituted azacyclic compound of formula Ia' and the intermediate compound thereof.

b. *State of the prior art and the level of the skill in the art.*

A compound encompassed by the instant formula 1a' is known (Lash, PTO-1449). An intermediate compound encompassed by the instant formula Xa is described by Bolte (PTO-1449). The selective synthesis with a metallated 2-alkenyl sulfoximines intermediate (page 1883, Table 1), followed by reductive elimination of the sulfur moiety from the S-aminooxosulfonium intermediate for the stereochemically controlled synthesis of the corresponding tetrahydrofuranyl compound has been described by Reggelin I and II (PTO-1449).

The level of the skilled in the chemical synthetic art is high.

c. *Predictability/unpredictability of the art.*

Unlike the mechanical art, the high degree of unpredictability is well recognized in the chemical synthetic art. A change in the structure of the compound may drastically affect the rate of the chemical reaction.

d. *Amount of guidance/working examples.*

The preparation of example compounds is limited to a monocyclic pyrrolidinyl or piperidinyl, or a bicyclic compound formed by R3 and R4 together being a C3-4 alkylene.

Starting materials and process of making thereof for the claimed compounds structurally different from the example compounds are not seen but required. Sources are particularly pertinent because absent sources, the public is offered mere language, rather than enablement. Ex parte Moersch 104 USPQ 122. In re Howarthe 210 USPQ 689.

e. *The breadth of the claims.*

Applicant's assertion that the process is applicable for the preparation of all the structurally diverse compound of formula Ia', especially those compounds wherein different substituents on the cyclic nitrogen ring together form aromatic or non-aromatic rings of various sizes and optionally substituted with N, S or O atom(s), does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability in the art and the limited working examples (paragraphs c, d above).

Art Unit: 1625

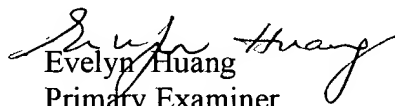
f. *Quantitation of undue experimentation.*

Since insufficient teaching and guidance have been provided in the disclosure, one of ordinary skill in the art, even with high degree of skill, would not be able to make and use all the compounds as claimed without undue experimentation, except for the intermediate compounds wherein  $R^1$ ,  $R^2$ ,  $R^{5-7}$ ,  $R^3$  and  $R^4$  are individual substituents or  $R^3$  and  $R^4$  together form a  $C_{3-4}$  alkylene, and the process of using the intermediate in the stereochemically controlled preparation of an isomerically pure substituted azacyclic compound.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 703-305-7247. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on 703-308-2439. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

  
Evelyn Huang  
Primary Examiner  
Art Unit 1625

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January 7, 2002